IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

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Applicant: Thomas L. Cantor *et alia*

Title: Methods, Kits & Antibodies for Detecting Parathyroid Hormone

Declaration of Dr. Ping Gao

Assistant Commissioner for Patents
Washington, DC 20231

DECLARATION OF DR. PING GAO

Pursuant to 37 CFR 1.68, I, Dr. Ping Gao, with a business address of Scantibodies Laboratory, Inc., 9336 Abraham Way, Santee, California, declare that:

1. I have an M. D. degree in basic and clinical medicine from Zhejiang University, China. I also have an M.D. degree in laboratory medicine from Ruprecht Karls University of Heidelberg, Germany.

2. I am an author of over 40 articles, including publications covering immunoassays, molecular biology, and calcium metabolism.

3. I have been involved in the field of the parathyroid hormone assays, for both commercial and research usage, for eight years. I have attended and made scientific presentations at seven scientific or trade conferences regarding calcium metabolism and parathyroid hormone (PTH) measurement over the last three years.

4. I have read and understand the above-identified patent application, the Office Action, and the references cited therein.

5. As to the first substantive obviousness issue in that Office Action, in my opinion, one of ordinary skill in the art reading the LePage article would not conclude that the presently claimed process is obvious. The present invention has unexpected benefits and utilities that are neither suggested nor recognized by LePage.

6. The present invention uncovers an unexpectedly high level of non-whole PTH in normal patients. Up to about 50% of an I-PTH value in normal patients can be attributed to non-whole PTH. This unexpectedly high level has direct consequences in that some normal patients are interpreted by I-PTH to be on the threshold of hyperparathyroidism (and thereby subjected to increase monitoring), but actually have a normal functioning parathyroid system that does not need such monitoring. Nowhere does LePage suggest that I-PTH values can be elevated to such a degree in normal patients.

7. The present invention unexpectedly is not in direct correlation with the I-PTH assays. In other words, the value from a whole PTH assay is not simply a consistent percentage value (from less than 10% to over 90%) of the I-PTH value. Nowhere does LePage suggest that not detecting non-(1-84) PTH would lead to such extensive variability from patient to patient.

8. The present invention unexpectedly also has the ability to allow the nephrologist to avoid potentially overdosing secondary hyperparathyroidism patients by using standard of care PTH suppressive therapy. In the past, I-PTH assays have been unable to assist accurately in the clinical assessment of low bone turnover disease versus high bone turnover disease, particularly if the patient is in the gray diagnostic zone of 100 to 400 pg/ml. Inaccurate assessment leads to unnecessary and patient damaging therapy. Certain patients having an apparently high PTH value are given PTH suppressive therapy, where in reality the patient has a normal 1-84 PTH value (described as whole PTH in the present claims). Thus, the patient is induced into an adynamic low bone turnover, tending to lead to renal osteodystrophy and soft tissue calcification, in particular coronary calcification. Nowhere does LePage address bone status predictive ability.

9. A fourth unexpected benefit of the present invention is the ability to detect almost all (96%) of the primary hyperparathyroidism patients in the mild (or early onset stage) as opposed to the I-PTH ability to detect only 72% of such patients. (I note that this magnitude of change in discrimination is equivalent to that which occurred between the earlier generation of mid-PTH assays and the introduction of the I-PTH assays.) This greater ability is especially important in view of the need to detect such patients as soon as possible so as to avoid irreversible loss of bone mass and organ (renal and cardiac) damage due to a high calcium blood level. Nowhere does LePage suggest that the non-(1-84) PTH fragment masks the ability of the I-PTH assay to discriminate amongst such patients. Nowhere does LePage suggest that such an enhanced degree of discrimination is possible.

10. A fifth unexpected benefit of the present invention is the ability for the clinician to avoid suspecting malignancy associated hypercalcemia (MAH), cancer, in patients that, in reality, have primary hyperpararthyroidism. For 24% of those patients with elevated blood calcium, I-PTH assays have led to suspecting MAH and resulted in a regimen of unnecessary cancer diagnostics, emotional trauma, and a delay, if not outright denial, in providing surgical therapy, the appropriate treatment for a hyperparathyroidism patient. Nowhere does LePage suggest that the non-(1-84) PTH fragment plays any role in such differentiation and provide a means to avoid improper treatment.

11. A sixth unexpected benefit of the present invention is increased timeliness in assessing the success of parathyroidectomy surgeries. The present invention is a faster intraoperative marker, being over five minutes faster than I-PTH assays in providing the waiting surgeon with an answer as to whether or not the excision of the parathyroid gland is complete. Nowhere does LePage suggest that an assay detecting whole PTH would be a faster intraoperative marker.

12. As to the second substantive obviousness issue in that Office Action, in my opinion, one of ordinary skill in the art reading the Campbell and LePage articles would not conclude that the presently claimed process is obvious. The present invention has unexpected benefits and utilities that are neither suggested nor recognized by either Campbell or LePage.

13. As to the third substantive obviousness issue in that Office Action, in my opinion, one of ordinary skill in the art reading my 1996 article would not conclude that the presently claimed process is obvious. My 1996 article is concerned with detecting the presence of N-terminal PTH fragments, namely, PTH 1-34 to PTH 1-38. We used a two-site immunoassay to detect such fragments, employing two (not just one) anti PTH 1-38 monoclonal antibodies. My 1996 article does not discuss detecting non-whole PTH. At that time, neither myself nor my co-authors knew of the non-whole PTH component in I-PTH assays. The previously listed unexpected benefits of the present invention are neither suggested nor recognized by me or my co-authors in 1996.

14. All statements made herein of my own knowledge are true, and that all statements made on information and belief are believed to be true. Furthermore, these statements are made with the knowledge that willful false statements and the like may jeopardize the validity of the present application or any patent issuing thereon and are punishable by fine, imprisonment, or both, under Section 1001 of Title 18 of the United States Code.

February 7, 2001

Dr. Ping Gao